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Studies on regional differences in pre-inspiratory lung volume and  
pre-inspiratory alveolar  $N_2$  concentration by a single breath method

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An essential function of the lung is to exchange gas between venous blood and air, so that gas distribution is important only in relation to blood distribution. Yet, no simple method of measuring regional differences in  $\dot{V}_A/\dot{Q}$  without employing radioactive gases has been introduced after West reported his method in 1957<sup>1)</sup>. Even though the measurement of uneven ventilation in the lung by a single breath  $O_2$  method has come into routine use since Fowler's report<sup>2)</sup> and it can provide an acceptable index of the presence of regional differences, this method cannot give any index corresponding to a particular region.

By the analysis of both Ar and  $N_2$  measured after a single inspiration of Ar- $O_2$  mixture, we constructed a single compartment model in order to calculate pre-inspiratory lung volume ( $V_{L\phi}$ ) and pre-inspiratory alveolar  $N_2$  concentration ( $F_{A\phi N_2}$ ), and we evaluated the changes in  $V_{L\phi}$  and  $F_{A\phi N_2}$  during the test expiration, as indices of regional differences in the ventilation and in the gas-exchange, respectively. Numerical values of  $V_{L\phi}$  and  $F_{A\phi N_2}$  could be also assigned to a series of functional units having regional differences.

Symbols and nomenclature

$CO_2$ , Ar,  $N_2$ ,  $O_2$  : carbon dioxide, argon, nitrogen and oxygen

$V_I$ ,  $V_E$  : inspired and expired volume

$V_{Da}$  : apparatus dead space

$V_D$  : series dead space

$V_{L\phi}$  : pre-inspiratory lung volume

$V_L$  : post-inspiratory lung volume

$IT$  : inspiratory time

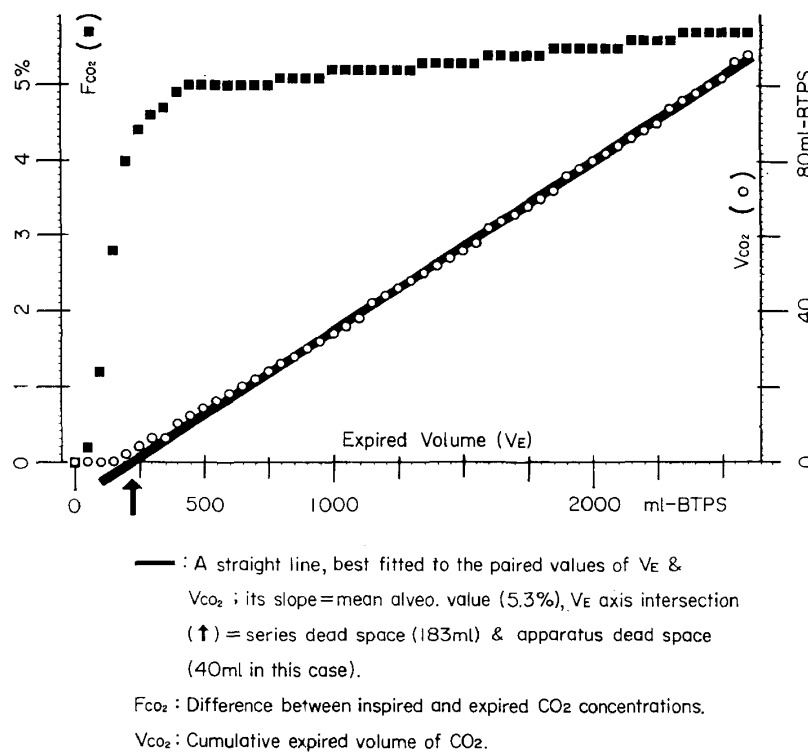
$F_I$  : concentration in inspired gas

$F_E$  : concentration in expired gas

$F_A$  : post-inspiratory alveolar concentration

$F_{A\phi N_2}$  : pre-inspiratory alveolar  $N_2$  concentration





**Fig. 2** Series dead space & Mean alveolar concentration, proposed by G. Cumming

derived from air on the assumption that their concentrations in the test expirate were proportional to  $F_{EAr}$  and to  $F_{EN_2}$ , respectively.

## 2) Definition of mean alveolar concentration (mean $F_A$ ), and series dead space ( $V_D$ ) (Fig. 2)

G. Cumming<sup>3)</sup> has found that there is a nearly linear relation between the whole expired volume and the cumulative expired volume for any particular gas components, i.e., the integrated product of the expiratory flow and the difference between concentrations in inspired and in expired gas, as shown in Fig. 2. Then, he applied this linearity to define the mean alveolar concentration which was necessarily accompanied by a new definition of a series dead space ( $V_D$ ).

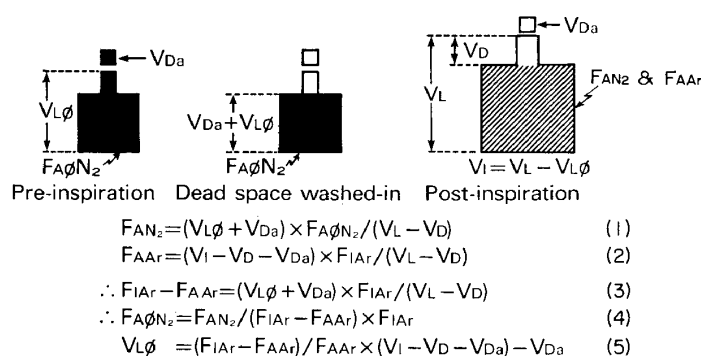
In the present study, a straight line was fitted to the paired values over the entire expiration in the first place, then the line was repeatedly re-calculated only beyond the  $V_E$  axis intersection of the previous line, until the line remained fixed.

The slope of this line gives the mean alveolar concentration and the point intersecting abscissa indicates the sum of the series dead space ( $V_D$ ) and the apparatus dead space ( $V_{Da}$ ).

## 3) Assumptions

When a single compartment model is assumed to include instantaneous complete gas mixing within the alveolar region, equations 1 and 2 can be given by the law of mass balance during the inspiration of  $Ar-O_2$  mixture which is free from  $N_2$  (Fig. 3). Subtraction of equation 2 from  $F_{IAr}$  gives equation 3, while dividing equation 1 by equation 3 and equation 3 by equation 2 give equations 4 and 5, respectively.

In the present study, the wash-out volume was assumed to be 3 times the series dead space, and the expirate beyond this wash-out volume was assumed to have the alveolar gas composition without inspired gas contamination.

**Fig. 3** Single compartment model

The pre-inspiratory alveolar  $N_2$  concentration ( $FA\phi N_2$ ) and the pre-inspiratory lung volume ( $V_L\phi$ ) were calculated by substitution of  $FEAR$  and/or  $FEN_2$  for  $FAAR$  and/or  $FAN_2$ , respectively in equations 4 and 5, continuously over the entire expiration. However, the changes were evaluated only in the range beyond the wash-out volume, and were assumed to reflect sequential emptying and varied contributions of various lung regions having regional differences, while the phase 3 was defined to begin just after the wash-out volume. Mean  $FA\phi N_2$  and mean  $V_L\phi$  were calculated by substitution of mean  $FAAR$  and/or mean  $FAN_2$  for  $FAAR$  and/or  $FAN_2$ , respectively in equations 4 and 5.

In appendix we refer to the critique of these calculations in the presence of continued gas exchange and the stratification in addition to the sequential emptying, because we neglected the former two factors and used  $FEAR$  and  $FEN_2$  in the place of  $FAAR$  and  $FAN_2$ .

#### 4) Discrimination of the phase 4 by the computer

This was done by using West's method<sup>4)</sup> with a slight modification: calculation of a straight line best fitted to the phase 3 was started from the wash-out volume in the place of 30% VC, because we defined the phase 3 to begin just after the wash-out volume.

## RESULTS

### 1) Series dead space ( $V_D$ ) (Table 1)

In Table 1, the average  $V_D$  values obtained by Cumming's method are presented to compare them with Fowler's  $V_D$  values<sup>5)</sup> predicted from Hart's formula<sup>6)</sup> and to find possible differences in those values among various gases.

In the procedures FRC-FRC+1L-FRC (a) and FRC-TLC-FRC (b), calculations were based on the data only between postinspiratory volumes (FRC+1 liter (a), TLC (b)) and FRC, though the actual test expiration was stopped not at FRC, but at RV.

In the case of FRC-FRC+1L-FRC procedure,  $V_D$  for  $N_2$  was smaller than that predicted by Hart in 3 out of 9 subjects, and  $V_D$  for  $CO_2$  was always found larger than those for Ar and for  $N_2$ , both of which were comparable.

On the contrary,  $V_D$  for  $N_2$  obtained by FRC-TLC-FRC procedure exceeded the predicted value in 3 out of 9 subjects. In FRC-TLC-FRC procedure,  $V_D$  was generally increased for all

**Table. 1** Comparison of series dead space with predicted values from Hart's formula, and among various gases.

Subject	AF	WS	KS	MF	YL	MO	MM	TL	KO
Age & Sex	24·F	29·F	31·M	30·M	39·M	29·M	25·M	29·M	38·M
Weight (kg)	42	57	56	75	80	57	75	78	85
Height (cm)	158	163	160	170	174	174	179	180	182
Prediction (1)	118±20	122±20	128±21	141±23	149±25	149±25	159±26	161±27	166±28
of V <sub>D</sub> (ml) (2)	103±21	131±27	129±27	164±34	173±36	131±27	164±34	169±35	182±38
a) FRC—FRC+1L—FRC procedure									
IT (sec)	9	1.8	5.6	5.8	2.8	5.4	4.4	4.2	3.7
V <sub>D</sub> (ml-BTPS)	CO <sub>2</sub>	95	116	120	121	158	136	157	126↓
	Ar	90	111	115	108↓	141	123	154	120↓
	N <sub>2</sub>	90	111	114	108↓	141	123	154	121↓
b) FRC-TLC-FRC procedure									
IT (sec)	14.5	8.7	19.1	14.2	13.6	8.8	11.4	14.7	21.4
V <sub>D</sub> (ml-BTPS)	CO <sub>2</sub>	104	134	201↑	225↑	184	259↑	273↑	228↑
	Ar	93	118	189↑	180	148	225↑	233↑	179
	N <sub>2</sub>	95	118	189↑	187	158	227↑	234↑	182

(1) =  $7.585 \times Ht^{2.363} \times 10^{-4} \pm 16.9\%$ , (2) =  $1.835 \times Wt + 26.59 \pm 21.2\%$  by Hart et al.

↑: higher, ↓: lower value than the predicted from whichever formula.

IT: Inspiratory time. V<sub>D</sub>: Series dead space. IT & V<sub>D</sub> are presented as average values for each subject.

gases and in all subjects. However, V<sub>D</sub> for CO<sub>2</sub> was always larger than V<sub>D</sub> for Ar or N<sub>2</sub>, while the latter two remaining comparable to each other, as was the case in the former procedure.

Since the accuracy of Fowler's method was confirmed in tests on the actual model with a known dead space<sup>7)</sup>, Cumming's method may systematically underestimate the actual anatomical geometry and dimension. However, Fowler's method is difficult to define the alveolar gas and deals with only the expirate of wash-out volume, forming the contrast with Cumming's method which can define the alveolar gas appropriately through the entire expiration. But, increase in V<sub>D</sub> due to the increased post-inspiratory lung volume, i.e., from FRC+1 liter up to TLC, was observed also in the present study as was found in studies using Fowler's method.<sup>5), 6)</sup> Consistently observed difference in V<sub>D</sub> between CO<sub>2</sub> and Ar or N<sub>2</sub> may be ascribed to the difference in alveolar plateaus, because Fowler's V<sub>D</sub> is believed to have practically no significant difference among various gases.<sup>8), 9)</sup>

## 2) FRC/TLC, RV/TLC and their regional differences detected during the phases 3 and 4 (Table 2)

In FRC-TLC-RV maneuver, V<sub>Lφ</sub> and (V<sub>Lφ</sub>+V<sub>i</sub>) correspond to FRC and TLC, respectively while V<sub>Lφ</sub> corresponds to RV in the case of RV-TLC-RV maneuver.

Since at TLC the volume of the lung units should be uniform throughout the lung, regional V<sub>Lφ</sub>/TLC is always proportional to the corresponding V<sub>Lφ</sub> in spite of the presence of regional difference in V<sub>Lφ</sub>. Thus, changes of V<sub>Lφ</sub>/(mean V<sub>Lφ</sub>+V<sub>i</sub>) during the phases 3 and 4 indicate

**Table. 2** FRC/TLC, RV/TLC and their regional differences detected during the phases 3 and 4.

$V_L\phi/(V_L\phi + V_I)$	Mean	Maximum	Minimum
a) FRC/TLC %	$50.8 \pm 6.8$	$66.1 \pm 8.5$	$44.9 \pm 5.7$
b) RV/TLC %	$22.2 \pm 3.9$	$30.8 \pm 6.3$	$19.9 \pm 3.3$

The values of a and b were obtained by FRC-TLC-RV and RV-TLC-RV maneuvers, respectively.

All figures are expressed as mean  $\pm$  SD.

$V_L\phi$ : Pre-inspiratory lung volume.  $V_I$ : Inspired volume.

**Table. 3** Mean  $FA\phi N_2$ , regional difference in  $FA\phi N_2$  detected during the phases 3 and 4, and mean R.Q.

	Mean $FA\phi N_2$	Maximum $FA\phi N_2$	Minimum $FA\phi N_2$	$FA\phi N_2$ gradient	Mean R.Q.
FRC-FRC+1L-RV	$80.8 \pm 1.8$ %	$81.2 \pm 1.9$ %	$79.0 \pm 1.2$ %	$2.1 \pm 1.1$ %	$0.80 \pm 0.18$
FRC-TLC-RV	$80.5 \pm 2.4$ %	$82.6 \pm 3.0$ %	$79.2 \pm 1.9$ %	$3.4 \pm 1.3$ %	$0.79 \pm 0.26$
t-test	NS	$P < 0.05$	NS	$P < 0.05$	NS

$FA\phi N_2$  gradient indicates the difference between maximum  $FA\phi N_2$  and minimum  $FA\phi N_2$ .

All figures are expressed as mean  $\pm$  SD.

the regional difference in FRC/TLC or RV/TLC, only disclosed by any existent sequential emptying. The changes were expressed as its maximum and minimum during the phases 3 and 4. FRC/TLC and RV/TLC were calculated and gave acceptable mean values of 50.8 and 22.2% with maxima of 66.1 and 30.8%, and minima of 44.9 and 19.9%, respectively.

$V_L\phi$  can be underestimated in the presence of a breath holding effect and unduly influenced by the gas from regions having larger contribution to the expirate, as discussed later. But, maximal and minimal values during the phases 3 and 4 were strikingly in accord with topographical data reported by Sutherland et al.<sup>10)</sup> who also controlled the inspiratory flow rate not to exceed 0.5 liter/sec, since the inspiratory flow rate has been shown to affect the ventilation distribution.<sup>11)</sup>

### 3) Mean $FA\phi N_2$ , regional difference in $FA\phi N_2$ detected during the phases 3 and 4, and mean R.Q. (Table 3)

Acceptable mean  $FA\phi N_2$  values of 80.0% and 80.5% were obtained in FRC-FRC+1L-RV and FRC-TLC-RV maneuvers, respectively. The same as in the case of  $V_L\phi$ ,  $FA\phi N_2$  change during expiration was thought to reflect its regional difference and was expressed as maximum and minimum during the phases 3 and 4. Then, the difference between the maximum and minimum was defined to be  $FA\phi N_2$  gradient.

The difference between  $FA\phi N_2$  gradient in FRC-FRC+1L-RV maneuver and that in FRC-TLC-RV maneuver, i.e.,  $2.1 \pm 1.1\%$  and  $3.4 \pm 1.3\%$ , respectively, was of statistical significance probably because of the increased maximum  $FA\phi N_2$  in the case of full inspiration to TLC (FRC-TLC-RV maneuver), during which the regions having lower R.Q. and resultant higher  $FA\phi N_2$  were recruited for ventilation, making more contribution to the expirate than in FRC-FRC+1L-RV maneuver. Maximum  $FA\phi N_2$  of 81.2% in FRC-FRC+1L-RV maneuver which approximated a tidal breath, was in concordance with topographical data from West's model.<sup>12),13)</sup>

Other numerical values of  $FA\phi N_2$  in Table 3 are also compatible with West's data, when

it is taken into account that the present method can be unduly influenced by the gas from well-ventilated regions and sensitive to intraregional inequalities. Calculations of mean R.Q. were made by substitution of mean FAO<sub>2</sub> and mean FACO<sub>2</sub> into the general alveolar gas equation. Acceptable values of 0.80 and 0.79 were obtained from FRC-FRC+1L-RV and FRC-TLC-RV maneuvers, respectively.

4) Changes in FECO<sub>2</sub>, FEN<sub>2</sub>, FAφN<sub>2</sub>, R.Q. and VLφ during expiration (Fig. 4, Fig. 5)

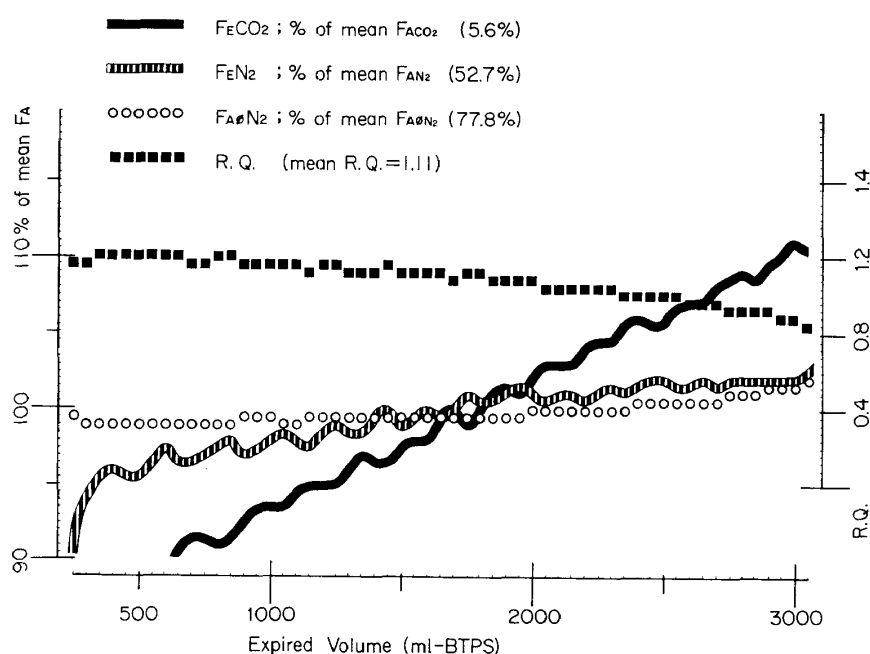
A representative case without discernible phase 4 was shown in Fig. 4a. Pre-inspiratory FAN<sub>2</sub> (FAφN<sub>2</sub>) made a gradually rising plateau until RV. But, FAφN<sub>2</sub> deflected downwards in agreement with FECO<sub>2</sub> deflection at systole of cardiogenic oscillations, where both FEN<sub>2</sub> and R.Q. had upward deflections. These oscillations were all reversed at diastole.

When the same maneuver developed the phase 4 in another subject (Fig. 4b), FAφN<sub>2</sub> and FECO<sub>2</sub> curves were deflected downwards there, corresponding with the abrupt upward deflection of FEN<sub>2</sub>.

For detailed study on the phase 4, the case with clearly discernible phase 4 was presented in Fig. 4c, which revealed recognizable upward deflection of R.Q. curve also. Thus, both phase 4 and systolic oscillations imposed downward deflections to FAφN<sub>2</sub> and FECO<sub>2</sub>, and upward deflections to FEN<sub>2</sub> and R.Q.

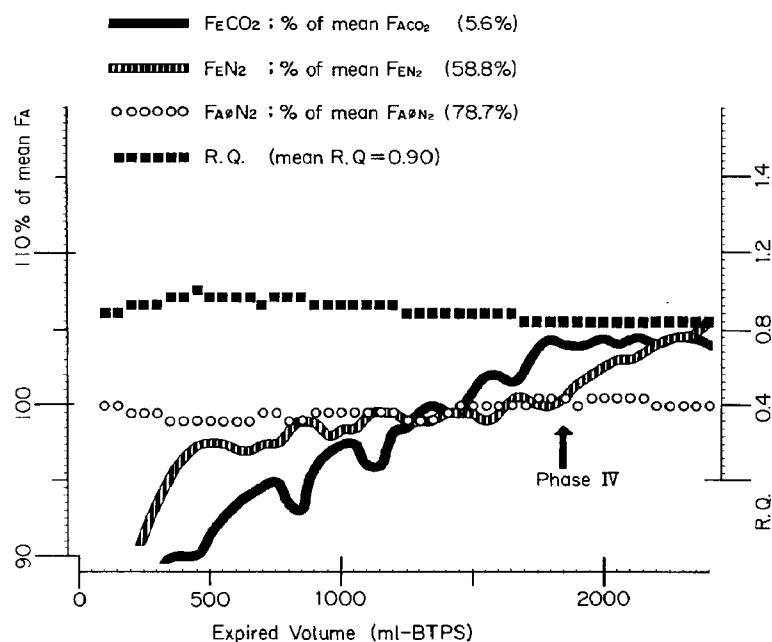
Additional remarks must be made here about the terminal stage of an apparent phase 3. At this stage, there were found striking rises in FAφN<sub>2</sub> and FECO<sub>2</sub> and striking falls of FEN<sub>2</sub> and R.Q. These changes were comparable to those found in the phase 4 though in the reciprocal way. This phenomenon is clearly visualized in Fig. 5b, which discloses a striking fall in VLφ in addition. This phenomenon can be best explained by the assumption that there may be considerable exaggeration of sequential emptying (and/or closure) well before the start of the phase 4,

**Fig. 4** Changes in FECO<sub>2</sub>, FEN<sub>2</sub>, pre-inspiratory alveolar N<sub>2</sub> concentration (FAφN<sub>2</sub>), and R. Q., during expiration.

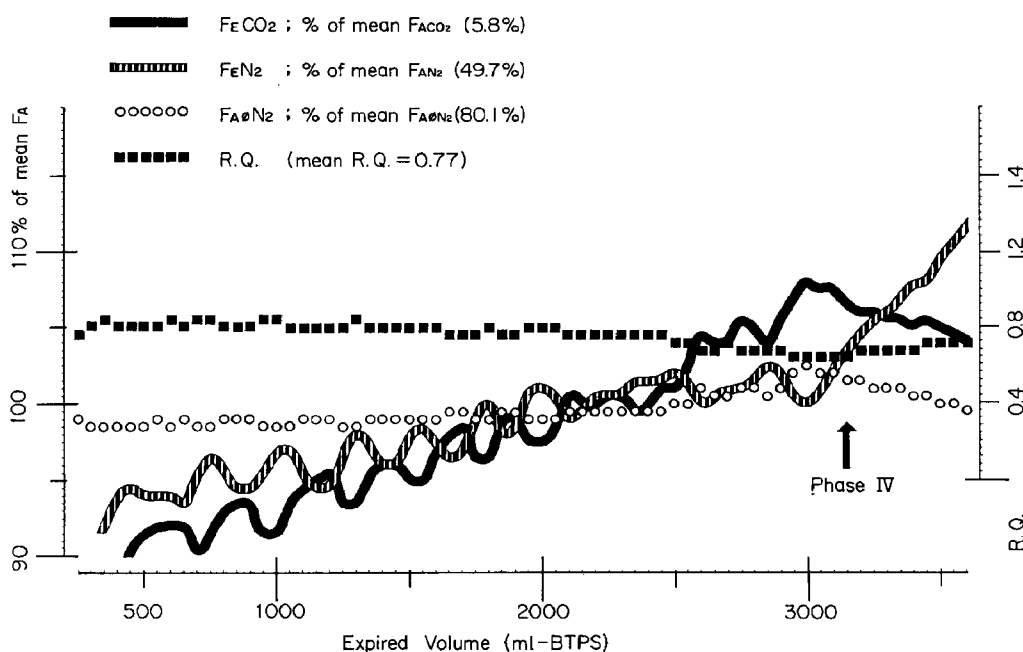


**Fig. 4a** Subject WS; FRC-FRC+1L-RV maneuver





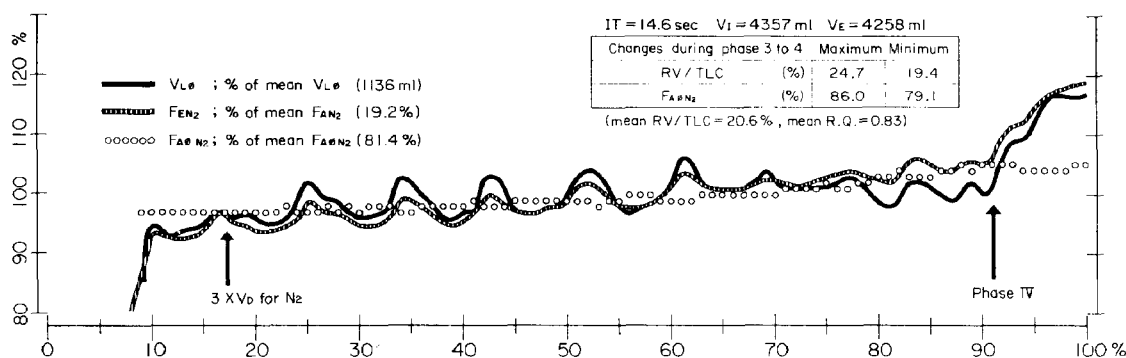
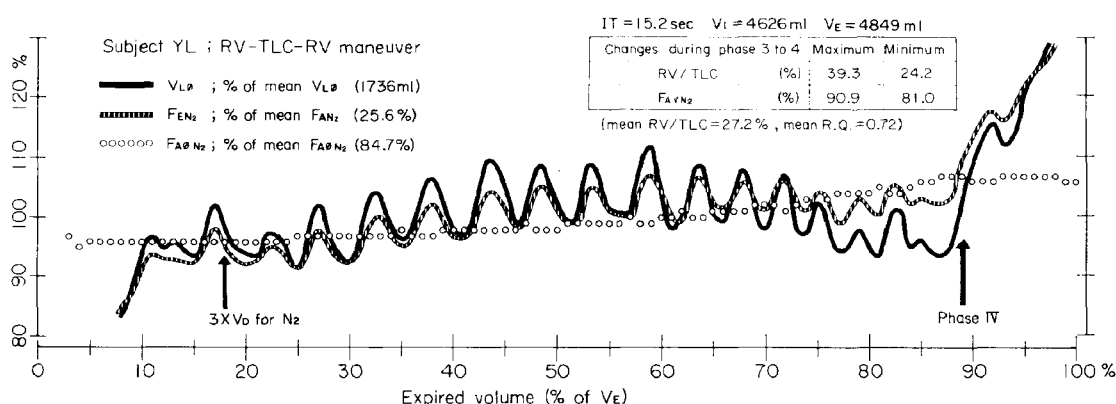
**Fig. 4b** Subject KS; FRC-FRC+1L-RV maneuver



**Fig. 4c** Subject KS; FRC-TLC-RV maneuver

and that the deflections of curves, in the opposite way to those in the phase 4, were caused by decreased contribution of lung regions having higher RV/TLC (or FRC/TLC) ratio, higher R.Q. with lower  $FA\phi N_2$  and higher  $FAN_2$ , all of which are characteristics of the upper regions in the erect healthy human lung. And, this is the usual explanation also for the diastolic oscillations.<sup>14)</sup> Even if the phase 3 of  $FEN_2$  record only made a slightly rising plateau as in the case of Fig. 5a, both  $FA\phi N_2$  and  $VL\phi$  showed the same trend as in Fig. 5b.

Fig. 5 is presented to investigate which of the two factors, i.e., the regional RV/TLC and regional  $FA\phi N_2$  differences, can be the principal determinant of the constitution of  $FEN_2$  recorded

**Fig. 5** Changes in pre-inspiratory lung volume ( $V_{L\phi}$ ),  $F_{EN_2}$  and pre-inspiratory alveolar N<sub>2</sub> concentration ( $FA\phi N_2$ ), during expiration.**Fig. 5a** Subject MO; RV-TLC-RV maneuver**Fig. 5b** Subject YL; RV-TLC-RV maneuver

by either O<sub>2</sub> or Ar-O<sub>2</sub> single breath method.

Since the breath holding effect during the test expiration makes  $V_{L\phi}$  falsely smaller and  $FA\phi N_2$  falsely larger than those obtained in the absence of this effect as discussed in appendix, general upward sloping of  $V_{L\phi}$  can be underestimated, and that of  $FA\phi N_2$  overestimated. On the other hand, relative changes in cardiogenic oscillations, terminal phase 3 and phase 4 are reasonably assumed to remain free from the breath holding effect because these changes take place rapidly.

Thus,  $F_{EN_2}$  changes in general sloping and in cardiogenic oscillations, terminal phase 3 and phase 4 can be concluded to reflect the regional difference of RV/TLC ratios rather than the difference in pre-inspiratory  $F_{AN_2}$  ( $FA\phi N_2$ ); the latter has less general sloping and shows relative change in the opposite way to  $F_{EN_2}$ , dampening the changes in  $F_{EN_2}$ .

## DISCUSSION AND CONCLUSION

Mixed alveolar gas is difficult to define because of contamination with gas from the anatomical dead space; the latter is usually estimated in practice by Fowler's method based on the arbitrarily adopted alveolar gas composition.

G. Cumming has proposed a new method<sup>3)</sup> to obtain mixed alveolar gas composition (called

mean alveolar concentration in the present study), by means of which calculations of mean values were made possible for pre-inspiratory lung volume ( $V_L\phi$ ), pre-inspiratory alveolar  $N_2$  ( $FA\phi N_2$ ) and respiratory quotient (R.Q.), although what was actually defined by this method remains to be appreciated.

Since the maximum exchange across the alveolar membrane is negligible for both  $N_2$  and Ar because of their low solubility<sup>15)</sup>, this exchange is assumed to introduce no significant error in this study including measurement of R.Q. following inspiration of Ar- $O_2$  mixture in the place of  $N_2$ - $O_2$  mixture, i.e., air.

The re-distribution of a dead space at the beginning of inspiration will affect  $FA\phi N_2$  and make its regional difference underestimated in the healthy lung, but was not taken into account in this paper.

It should be pointed out that the present study was concerned about the regional differences in R.Q. that could be produced by the inspired gas to give any particular alveolar gas compositions, as was the case in West's report.<sup>1)</sup> Therefore, R.Q. in the present study is entirely different from the instantaneous  $R^{16)}$  that could be produced by any particular alveolar gas compositions in a homogeneous alveolar gas phase and in the absence of sequential emptying.

In the present study, the direction of R.Q. deflection during expiration apparently corresponded with  $FA\phi N_2$  deflection though in a reciprocal manner. However, allowance should be made for some fall in R.Q. due to gas exchange continuing during expiration in order to derive accurate index of  $\dot{V}_A/\dot{Q}$  inequality from R.Q. or its substitutes. This gas exchange effect was reported by Meade et al.<sup>17)</sup> to account for 2/3 of the apparent % change in  $\dot{V}_A/\dot{Q}$  between 750 ml and 1250 ml samples.

In appendix, we discuss this breath holding effect of continued gas exchange as well as of decaying stratification during the time lapse between early and late expirate though only in the qualitative way.

Nevertheless, such relative changes within a short time as cardiogenic oscillations and striking deflections in terminal phase 3 and phase 4 are reasonably assumed to be produced not by this breath holding effect, but by accentuated sequential emptying and/or air way closure. The apparent decrease in  $FEN_2$  in the terminal phase 3 also contradicts the effects of continued gas exchange.

When changes in  $FA\phi N_2$  and  $V_L\phi$  were compared with the topographical differences found in the erect healthy human lung, it was assured that both systolic cardiogenic oscillations and the phase 4 deflection were related with markedly increased contribution of the upper lung regions. On the other hand, the deflection in the terminal phase 3 that has been neglected so far, as well as diastolic oscillations was concluded to reflect the decreased contribution of upper lung regions, forming the contrast to the phase 4 and systolic oscillations.

As for  $FEN_2$  record on a conventional single breath  $O_2$  method,  $FEN_2$  was found to be governed by regional ventilation distribution, as has been advocated since Fowler's report was published.<sup>2)</sup>

On the contrary,  $FA\phi N_2$  change was directed to dampen  $FEN_2$  change.

In conclusion, it was suggested that though without direct topographical informations, the present method could provide measurements for regional differences and mean overall values of both ventilation and pre-existing alveolar  $N_2$  concentration reflected in the test expirate. More-

over, we have afforded a new insight into the mechanism that underlies the conventional FEN<sub>2</sub> record.

## APPENDIX

Rearranging equation 5 in Fig. 3 gives

$$V_L\phi = (F_{IAr}/F_{AAr} - 1) \times (V_I - V_D - V_{Da}) - V_{Da} \quad (6)$$

Dividing equation 1 by equation 2 gives

$$F_{AN_2}/F_{AAr} = (V_L\phi + V_{Da}) \times F_{A\phi N_2} / (V_I - V_D - V_{Da}) / F_{IAr} \quad (7)$$

If a breath holding effect is taken into account during a test expiration, then continued gas exchange should be associated with an increase in F<sub>AAr</sub> because of less dilution or more concentration due to lowering of R.Q. induced by it. Thus, F<sub>IAr</sub>/F<sub>AAr</sub> in equation 6 becomes smaller with falsely smaller V<sub>L</sub>φ, while F<sub>A</sub>φN<sub>2</sub> will be calculated falsely larger, because F<sub>AN<sub>2</sub></sub>/F<sub>AAr</sub> in equation 7 is believed to be constant, though each gas is affected in the same way by continued gas exchange.<sup>15)</sup>

In the second place, since stratification, if any, will be reduced by a breath holding effect, F<sub>AAr</sub> will become larger in the later expirate with the axial gradient for Ar, i.e. (F<sub>IAr</sub> - F<sub>AAr</sub>), reduced, leading to falsely smaller V<sub>L</sub>φ in this time also. But, because decaying of stratification is proportional to the axial concentration gradient, i.e., (F<sub>AN<sub>2</sub></sub> - F<sub>IN<sub>2</sub></sub>) for N<sub>2</sub> and (F<sub>IAr</sub> - F<sub>AAr</sub>) for Ar, (F<sub>AN<sub>2</sub></sub> - F<sub>IN<sub>2</sub></sub>)/(F<sub>IAr</sub> - F<sub>AAr</sub>) remains constant. When F<sub>IN<sub>2</sub></sub> = 0 as in the present study, F<sub>AN<sub>2</sub></sub>/(F<sub>IAr</sub> - F<sub>AAr</sub>) in equation 4 in Fig. 3 becomes also constant and thus, F<sub>A</sub>φN<sub>2</sub> is not affected by the presence of stratification.

In summary, a breath holding effect, whether by means of continued gas exchange or of decaying stratification, is expected to make the calculated V<sub>L</sub>φ falsely smaller, but F<sub>A</sub>φN<sub>2</sub> will become falsely larger only in the presence of continued gas exchange.

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